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 Use of macrolide compounds for manufacturing agent for
 preventing or treating pain (Eng)
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 Addnl. Data: KELLY J S, MCQUEEN D S
 1999.07.02 1999WO-JP03602

NOVELTY

Use of macrolide compounds for manufacturing an agent for preventing or treating pain.

ACTIVITY

Analgesic; immunosuppressive; antimicrobial. Test compound, FR900506, was tested for analgesic properties on joint hyperalgesia in young, adult, male Lister Hooded rats (Charles Rivers). Drug treatment was by rubbing 75 mg ointment A [containing FK506 Substance (0.1 g), propylene carbonate (5 g), liquid paraffin (11 g), solid paraffin (3 g), white beeswax (3.5 g) and white petrolatum (q.s. to 100 g)] or vehicle B into the left ankle joint twice daily for 5 days.

B(6-E5, 14-A1, 14-C1, 14-C9, 14-G2, 14-G2C) .4

Measurements were made 10 minutes after the afternoon application of ointment. Results showed that FR900506 has analgesic properties when topically applied to chronically hyperalgesic arthritic joints in rats.

MECHANISM OF ACTION

None given.

USE

Used to manufacture agents for preventing or treating pain particularly pain caused by arthritis (claimed) e.g. rheumatoid arthritis, acute rheumatic arthritis, gouty arthritis, psoriatic arthritis, arthralgia (intermittent or periodic), hyperalgesia, allodynia (senile pruritis), and cutaneous manifestations of algesia caused by various diseases. Also used to treat or prevent rejection reactions by transplantation of organs or tissues, graft-versus-host disease, autoimmune diseases and infectious diseases.

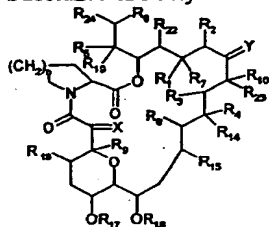
ADMINISTRATION

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Administration is topical (claimed) as well as enteral, intravenous, intramuscular or parenteral. Administration is to livestock mammals (cows, horses), domestic animals (dogs, cats, rats) and humans. Daily dosage is 0.0001-1,000 (0.001-500; 0.01-100) mg. Single doses contain 0.001-0.01; 0.2-0.5; 1; 5; 10; 50; 100; 250; 500 mg. Daily dose for chronic administration is 0.1-0.3 mg/kg/day.

TECHNOLOGY FOCUS

Organic Chemistry - Preferred Compounds - Macrolides are of formula (I) or their pharmaceutically acceptable salts. Macrolide is FK 506 Substance or its hydrate.



(I)

R_1 and R_2 , R_3 and R_4 , R_5 and R_6 = two adjacent H atoms (R_2 is also alkyl) or forms a bond between C to which they are attached;
 R_7 = H, optionally protected hydroxy, alkoxy or, together with R_1 , may form oxo;
 R_8 , R_9 = H or hydroxy;
 R_{10} = H, alkyl or alkenyl (optionally substituted by hydroxy groups) or alkyl substituted by oxo;
 X = O, H and OH, H and H or forms CH_2O ;
 Y = O, H and OH, H and H or form $NNR_{11}R_{12}$ or NOR_{13} ;
 R_{11} , R_{12} = H, alkyl, aryl or tosyl;
 R_{13} - R_{19} , R_{22} , R_{23} = H or alkyl;
 R_{24} = optionally substituted ring system containing one or more heteroatoms;
 n = 1-2; and
 Y , R_{10} and R_{23} together with the C to which they are attached form (un)saturated 5-6-membered, N-, S- and/or O-containing heterocycle optionally substituted by one or more of alkyl, OH, alkoxy, benzyl, $CH_2Se(C_6H_5)$ or alkyl substituted by one or more hydroxy groups.
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Rechtsstandsinformation

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(21) International Application Number: PCT/JP99/03602 (22) International Filing Date: 2 July 1999 (02.07.99) (30) Priority Data: 9814640.0 6 July 1998 (06.07.98) GB (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): KELLY, John, S. [GB/GB]; University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ (GB). MCQUEEN, Daniel, S. [GB/GB]; University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ (GB). (74) Agent: TABUSHI, Eiji; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP).		(81) Designated States: BR, CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE OF FK506 AND RELATED MACROLIDES IN THE MANUFACTURE OF A MEDICAMENT FOR TREATMENT OR PREVENTION OF PAIN (57) Abstract <p>Macrolide compounds, such as the FK506 Substance and its related compounds are provided for use as an analgesic, particularly, a topical analgesic. Composition containing such compounds is also disclosed.</p>		

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DESCRIPTION

USE OF FK506 AND RELATED MACROLIDES IN THE MANUFACTURE OF A MEDICAMENT FOR TREATMENT OR PREVENTION OF PAIN

TECHNICAL FIELD

This invention relates to a new use of macrolide compounds as an analgesic.

BACKGROUND ART

The macrolide compound and its pharmaceutically acceptable salt for use in accordance with this invention is known to have excellent immunosuppressive activity, and, as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs.-host diseases, autoimmune diseases, and so on [EP-A-0184162, EP-A-0323042, etc].

DISCLOSURE OF INVENTION

The inventors of this invention have surprisingly found that the macrolide compounds mentioned herein below have an analgesic effect, especially topical analgesic effect, and thereby are useful as an analgesic.

Accordingly, this invention provides a new use of the macrolide compounds as an analgesic.

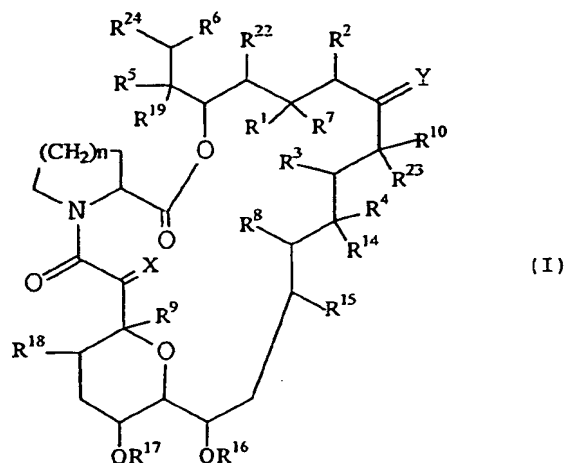
Further, this invention provides an analgesic, which comprises the macrolide compounds.

Still further, this invention provides a method for preventing or treating pain, which comprises administering said macrolide compounds to mammals.

The term "macrolide compound" for use in accordance with the invention is the generic name of compounds with 12 members or more, which belong to macrocyclic lactones.

As a particular example of the macrolide compound, the

tricyclic compound of the following formula (I) can be exemplified.



(wherein each of adjacent pairs of R^1 and R^2 , R^3 and R^4 , and R^5 and R^6 independently

(a) is two adjacent hydrogen atoms, but R^2 may also be an alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R^7 is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R^1 ;

R^8 and R^9 are independently a hydrogen atom or a hydroxy group; R^{10} is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula $-\text{CH}_2\text{O}-$;

Y is an oxo group, (a hydrogen atom and a hydroxy group),

(a hydrogen atom and a hydrogen atom), or a group represented by the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{22} and R^{23} are independently a hydrogen atom or an alkyl group;

R^{24} is an optionally substituted ring system which may contain one or more heteroatoms;

n is an integer of 1 or 2; and

in addition to the above definitions, Y , R^{10} and R^{23} , together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and an alkyl substituted by one or more hydroxy groups.

Preferable R^{24} may be cyclo(C_{3-7})alkyl group, and the following ones can be exemplified.

(a) a 3,4-di-oxo-cyclohexyl group;

(b) a 3- R^{20} -4- R^{21} -cyclohexyl group,

in which R^{20} is hydroxy, an alkoxy group, an oxo group, or a $-OCH_2OCH_2CH_2OCH_3$ group, and

R^{21} is hydroxy, $-OCN$, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminoxyloxy, an azido group, p-tolyloxythiocarbonyloxy,

or $R^{25}R^{26}CHCOO-$,

in which R^{25} is optionally protected hydroxy

or protected amino, and

R^{26} is hydrogen or methyl, or

R^{20} and R^{21} together form an oxygen atom in an-
epoxide ring; or

(c) cyclopentyl group substituted by methoxymethyl, optionally
protected hydroxymethyl, acyloxymethyl

(in which the acyl moiety optionally contains either a
dimethylamino group which may be quaternized, or a
carboxy group which may be esterified), one or more amino
and/or hydroxy groups which may be protected, or
aminooxalyloxymethyl. A preferred example is a 2-
formyl-cyclopentyl group.

The definitions used in the above general formula (I) and
the specific and preferred examples thereof are now explained
and set forth in detail.

The term "lower" means, unless otherwise indicated, a
group having 1 to 6 carbon atoms.

Preferable examples of the "alkyl groups" and an alkyl-
moiety of the "alkoxy group" include a straight or branched chain
aliphatic hydrocarbon residue, for example, a lower alkyl group
such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl,
pentyl, neopentyl and hexyl.

Preferable examples of the "alkenyl groups" include a
straight or branched chain aliphatic hydrocarbon residue having
one double-bond, for example, a lower alkenyl group such as vinyl,
propenyl (e.g., allyl group), butenyl, methylpropenyl, pentenyl
and hexenyl.

Preferable examples of the "aryl groups" include phenyl, tolyl, xylyl, cumenyl, mesityl and naphthyl.

Preferable protective groups in the "protected hydroxy groups" and the "protected amino" are 1-(lower alkylthio)-(lower)alkyl group such as a lower alkylthiomethyl group (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more preferably C_1 - C_4 alkylthiomethyl group, most preferably methylthiomethyl group;

and a trisubstituted silyl group such as a tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylysilyl, etc.) or lower alkyl-diarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl, etc.), more preferably tri(C_1 - C_4)alkylsilyl group and C_1 - C_4 alkyldiphenylsilyl group, most preferably tert-butyldimethylsilyl group and tert-butyldiphenylsilyl group; and an acyl group such as an aliphatic, aromatic acyl group or an aliphatic acyl group substituted by an aromatic group, which are derived from a carboxylic acid, sulfonic acid or carbamic acid.

Examples of the aliphatic acyl groups include a lower alkanoyl group optionally having one or more suitable substituents such as carboxy, e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.;

a cyclo(lower)alkoxy(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkyl, e.g., cyclopropyloxyacetyl, cyclobutyloxypropionyl,

cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxypentanoyl, menthyloxyhexanoyl, etc.; a camphorsulfonyl group; or a lower alkylcarbamoyl group having one or more suitable substituents such as carboxy or protected carboxy, for example, carboxy(lower)alkylcarbamoyl group (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), tri-(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl group (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyl dimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.) and so on.

Examples of the aromatic acyl groups include an aroyl group optionally having one or more suitable substituents such as nitro, e.g., benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.; and an arenesulfonyl group optionally having one or more suitable substituents such as halogen, e.g., benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.

Examples of the aliphatic acyl groups substituted by an aromatic group include ar(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkoxy or trihalo(lower)alkyl, e.g., phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.

More preferable acyl groups among the aforesaid acyl groups are C₁-C₄ alkanoyl group optionally having carboxy, cyclo(C₅-C₆)alkoxy(C₁-C₄)alkanoyl group having two (C₁-C₄) alkyls at the cycloalkyl moiety, camphorsulfonyl group, carboxy-(C₁-C₄)alkylcarbamoyl group, tri(C₁-C₄)alkylsilyl(C₁-C₄)alkoxycarbonyl(C₁-C₄)-alkylcarbamoyl group, benzoyl group optionally having one or two nitro groups, benzenesulfonyl group having halogen, or phenyl(C₁-C₄)alkanoyl group having C₁-C₄ alkoxy and trihalo(C₁-C₄)alkyl group. Among these, the most preferable ones are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

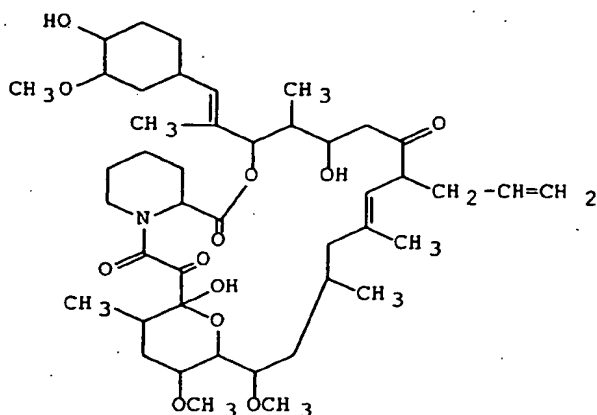
Preferable examples of the "5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring" include a pyrrolyl group and a tetrahydrofuryl group.

"A heteroaryl which may be substituted by suitable substituents" moiety of the "heteroaryloxy which may be substituted by suitable substituents" may be the ones exemplified for R¹ of the compound of the formula of EP-A-532,088, with preference given to 1-hydroxyethylindol-5-yl, the disclosure of which is incorporated herein by reference.

The ticyclic compounds (I) and its pharmaceutically acceptable salt for use in accordance with this invention are well known to have excellent immunosuppressive activity, antimicrobial activity and other pharmacological activities and, as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs-

host diseases, autoimmune diseases, and infectious diseases [EP-A-0184162, EP-A-0323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059, etc.], the disclosures of which are incorporated herein by reference.

Particularly, the compounds which are designated as FR900506 (=FK506), FR900520 (ascomycin), FR900523, and FR900525 are products produced by microorganisms of the genus Streptomyces, such as Streptomyces tsukubaensis No. 9993 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit October 5, 1984, accession number FERM BP-927] or Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit January 12, 1985, accession number FERM - BP-928] [EP-A-0184162]. The FK506 (general name: tacrolimus) of the following chemical formula, in particular, is a representative compound.



Chemical name: 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone

The preferred examples of the tricyclic compounds (I) are the ones, wherein each of adjacent pairs of R³ and R⁴ or R⁵ and R⁶ independently form another bond formed between the carbon atoms to which they are attached;

each of R⁸ and R²³ is independently a hydrogen atom;

R⁹ is a hydroxy group;

R¹⁰ is a methyl group, an ethyl group, a propyl group or an allyl group;

X is (a hydrogen atom and a hydrogen atom) or an oxo group;

Y is an oxo group;

each of R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²² is a methyl group;

R²⁴ is a 3-R²⁰-4-R²¹-cyclohexyl group,

in which R²⁰ is hydroxy, an alkoxy group, an oxo group, or a -OCH₂OCH₂CH₂OCH₃ group, and

R²¹ is hydroxy, -OCN, an alkoxy group, a

heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$, - in which R^{25} is optionally protected hydroxy or protected amino, and R^{26} is hydrogen or methyl, or R^{20} and R^{21} together form an oxygen atom in an epoxide ring; and n is an integer of 1 or 2.

The most preferable tricyclic compounds(I) is, in addition to FK506, ascomycin derivatives such as halogenated-ascomycin (e.g., 33-epi-chloro-33-desoxyascomycin), which is disclosed in EP 427,680, example 66a.

The tricyclic compounds(I) has a similar basic structure, i.e., tricyclic macrolide structure, and at least one of the similar biological properties (for example, immunosuppressive activity).

The tricyclic compounds(I) may be in a form of its salt, which includes conventional non-toxic and pharmaceutically acceptable salt such as the salt with inorganic or organic bases, specifically, an alkali metal salt such as sodium salt and potassium salt, an alkali earth metal salt such as calcium salt and magnesium salt, an ammonium salt and an amine salt such as triethylamine salt and N-benzyl-N-methylamine salt.

With respect to the macrolide compound used in the present invention, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom(s) or double bond(s), and such conformers and isomers are also included within the scope of macrolide compound in the present invention. And further, the macrolide compounds can be in the form of a solvate or pro-drug, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

The macrolide compounds usable in the present invention may be administered as pure compounds or mixtures of compounds or preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the tricyclic compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external(topical), enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, eye drops, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), ointment, aerosol sprays, cream, skin plasters, patches and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary,

stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

For applying this composition to a human, it is preferable to apply it by topical, especially by external, administration, particularly in the form of ointment, gel, lotion, aerosol sprays, cream, skin plasters or patches.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.0001-1000 mg, preferably 0.001-500 mg and more preferably 0.01-100 mg. of the active ingredient is generally given for treating diseases, and an average single dose of about 0.001-0.01mg, 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses for chronic administration in humans will be in the range of about 0.1-0.3 mg/kg/day.

Especially, when applying externally, the recommended proportion of macrolide compound in the pharmaceutical composition is 0.001~20% (w/w), preferably 0.01~10% (w/w), of the total composition. And further, the macrolide compounds can be applied, simultaneously, separately or sequentially, with other agents having analgesic activity or immunosuppressive activity; such as, malononitrilamides (HMR 1279, HMR1715, etc), mycophenolate mofetil (CellCept), steroids, Azathiopurine, and

so on.

The following examples illustrate the present invention in further detail. It should be understood that those examples are not intended to limit the scope of the invention.

Example 1

FK506 Substance	0.1 g
propylene carbonate	5.00 g
liquid paraffin	11.0 g
solid paraffin	3.0 g
white bees wax	3.5 g
white petrolatum	q.s. (to 100.0 g)

The ointment composed of the above ingredients was prepared in a similar manner to that of the Example 1 described in EP-A-0474126.

Example 2

FK 506 Substance	1 g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1 g
Lactose	2 g
Croscarmellose sodium (Ac-Di-Sol)	1 g

The FK 506 Substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Lactose (2 g) and croscarmellose sodium (Trade Mark: Ac-Di-Sol, maker: Asahi Chemical Industry) were homogeneously suspended to this solution, and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2

minutes by coffee mill and then passed through a sieve (32 mesh) to give the solid dispersion composition of FK 506 Substance (5 g). This composition was capsulated by a conventional manner to provide capsules containing 1 mg or 5 mg of FK 506 Substance per each capsule. This composition can be prepared in a similar manner to that of EP-A-0240773.

Example 3

Experiment

Young adult male Lister Hooded rats (Charles Rivers, UK) were maintained under standard animal house conditions, maximum 3 animals per cage, with access to food and water *ad lib*.

Unilateral arthritis was induced using the method described by Donaldson et al, J. Neurosci. Methods 31; 681-691 (1993). Briefly, the rat was anaesthetized with halothane (5% in oxygen) and 0.15 ml of Freund's complete adjuvant (Sigma; 1mg/ml heat killed mycobacterium tuberculosis) injected sub-dermally around the left ankle (tibio-tarsal) joint.

Measurement of pressure evoking reflex withdrawal of the limb when the joint was squeezed was undertaken using an pressure transducer (designed in-house) linked to a chart recorder and the mean of three consecutive pressure measurements made on each ankle, the right (control) joint being measured first. A tape measure was used for determining ankle circumference, and an infrared thermometer held against the joint used to provide a measure of temperature. Rats were weighed to provide an indication of general health.

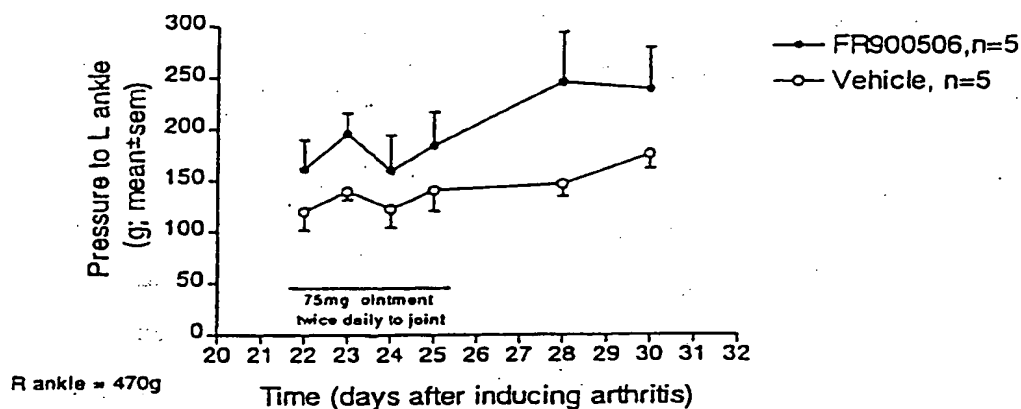
Drug treatment involved rubbing 75mg (pre-weighed) of ointment A, which is the same one prepared by the above-identified Example 1, or B (vehicle) into the left ankle joint

twice daily (at 09:00, 14:00) for five days. For the acute study, treatment started 24hrs before arthritis was induced (5 rats received FR900506, 5 received vehicle). For the chronic study, treatment started 21 days post-adjuvant, again with 5 rats per group. Measurements were made approximately 10 minutes after the afternoon application of ointment and took 30 minutes to complete.

Results

The analgesic effect of FR900506 is shown in Fig. 1. FR900506 has analgesic properties when applied topically to chronically hyperalgesic arthritic joints in the rat.

Fig. 1 Influence of FR900506 on joint hyperalgesia



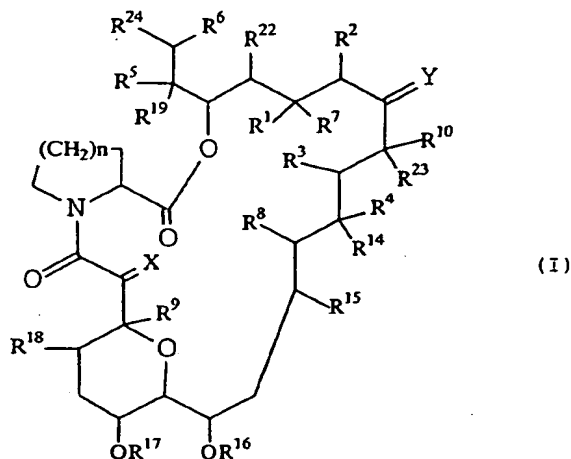
The macrolide compound or its pharmaceutically acceptable salt was proved to have the analgesic effect, especially the topical analgesic effect, and thereby when administered systemically or topically is useful for treating and/or

preventing pain(e.g., pain caused by arthritis(rheumatoid arthritis, acute rheumatic arthritis, gouty arthritis, psoriatic arthritis, etc)); arthralgia (intermittent arthralgia, periodic arthralgia, etc); hyperalgesia; allodynia (senile pruritus, etc); cutaneous manifestation of algesthesia caused by various diseases; and so on.

The patents, patent applications and publications cited herein are incorporated by reference.

CLAIMS

1. A use of macrolide compounds for manufacturing an agent for preventing or treating pain.
2. The use of Claim 1, in which the macrolide compounds is the tricyclic compounds of the following formula (I):



(wherein each of adjacent pairs of R^1 and R^2 , R^3 and R^4 , and R^5 and R^6 independently

(a) is two adjacent hydrogen atoms, but R^2 may also be an alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R^7 is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R^1 ;

R^8 and R^9 are independently a hydrogen atom or a hydroxy group;

R^{10} is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a

hydrogen atom and a hydrogen atom), or a group represented by the formula $-\text{CH}_2\text{O}-$;

Y is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula $\text{N}-\text{NR}^{11}\text{R}^{12}$ or $\text{N}-\text{OR}^{13}$;

R^{11} and R^{12} are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{22} and R^{23} are independently a hydrogen atom or an alkyl group;

R^{24} is an optionally substituted ring system which may contain one or more heteroatoms;

n is an integer of 1 or 2; and

in addition to the above definitions, Y, R^{10} and R^{23} , together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula $-\text{CH}_2\text{Se}(\text{C}_6\text{H}_5)$, and an alkyl substituted by one or more hydroxy groups; or its pharmaceutically acceptable salt.

3. A method for preventing or treating pain, which comprises administering macrolide compounds to mammals.

4. A pharmaceutical composition for preventing or treating pain, which comprises macrolide compounds in admixture with a carrier or excipient.

5. A use of the macrolide compounds for preventing or treating pain.

6. The macrolide compound used in Claims 1 to 5 is FK 506 Substance or its hydrate.

7. A use of macrolide compounds for manufacturing an

analgesic for topical use.

8. A use of macrolide compounds for manufacturing a medicament for preventing or treating pain caused by arthritis.

9. The use of Claim 8, in which the medicament is for topical administration.

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